(FILE 'HOME' ENTERED AT 15:45:56 ON 03 DEC 1999)

FILE 'REGISTRY' ENTERED AT 15:46:04 ON 03 DEC 1999

L1 0 S POLYOXYETHYLENE/CN
L2 0 S POLYOXYETHYLENE/CN
E POLYOXYLATE?/CN
L3 1 S E4
L4 0 S L3 AND (ESTER? OR ALCOHOL? OR PHENOL?)

FILE 'USPATFULL, CAPLUS' ENTERED AT 15:48:57 ON 03 DEC 1999

L5 90 S L3
L6 332632 S LIPOSOME? OR EMULSION? OR MICROEMULSI? OR MICROCAPSULE? OR
MI
L7 5 S L5 AND L6

FILE 'REGISTRY' ENTERED AT 15:51:24 ON 03 DEC 1999

L8 0 S POLYSORBATE/CN
L9 1 S POLYSORBATE 80/CN
L10 0 S OLETH-20/CN
L11 0 S OLETH20/CN
L12 1 S OLETH/CN
L13 3 S POLOXAMER?/CN

FILE 'USPATFULL, CAPLUS, MEDLINE' ENTERED AT 15:53:17 ON 03 DEC 1999

L14 15176 S L9 OR L12 OR L13
L15 3640 S L6 AND L14
L16 1178 S HOMOGENEOUS (10W) CLEAR
L17 291798 S TRANSPARENT?
L18 32751 S CLEAR (5W) (SOLUTION OR EMULSION OR MIXTURE)
L19 343 S (L18 OR L16 OR L17) AND L15
L20 8384 S NANODISPERSION? OR NANOPARTICLE?
L21 10 S L20 AND L19

L21 ANSWER 1 OF 10 USPATFULL
AN 1999:58922 USPATFULL
TI Topical preparation containing a suspension of solid lipid particles
IN De Vringer, Tom, Zoetermeer, Netherlands
PA Yamanouchi Europe B.V., Netherlands (non-U.S. corporation)
PI US 5904932 19990518
AI US 1995-473121 19950607 (8)
RLI Continuation of Ser. No. US 1993-131480, filed on 4 Oct 1993, now abandoned which is a continuation of Ser. No. US 1992-857467, filed on 25 Mar 1992, now abandoned
PRAI EP 1991-200664 19910325
DT Utility
LN.CNT 814
INCL INCLM: 424/450.000
INCLS: 424/401.000; 424/489.000; 424/490.000; 424/502.000
NCL NCLM: 424/450.000
NCLS: 424/401.000; 424/489.000; 424/490.000; 424/502.000
IC [6]
ICM: A61K009-00
ICS: A61K009-14
EXF 424/450; 424/401; 424/489-490; 424/502
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 2 OF 10 USPATFULL
AN 1998:25218 USPATFULL
TI Nanosuspensions for intravenous administration
IN Weder, Hans Georg, Ruschlikon, Switzerland
van Hoogevest, Peter, Riehen, Switzerland
PA Novartis Corporation, Summit, NJ, United States (U.S. corporation)
PI US 5726164 19980310
AI US 1996-619068 19960320 (8)
PRAI CH 1995-804 19950321
DT Utility
LN.CNT 576
INCL INCLM: 514/080.000
INCLS: 514/103.000
NCL NCLM: 514/080.000
NCLS: 514/103.000
IC [6]
ICM: A61K031-35
ICS: A61K031-55; A61K031-40
EXF 514/103; 514/80
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 3 OF 10 USPATFULL
AN 97:117716 USPATFULL
TI Nanoemulsion of the oil water type, useful as an ophthalmic vehicle and process for the preparation thereof
IN Valdivia, Francisco Javier Galan, Barcelona, Spain
Dachs, Anna Coll, Barcelona, Spain
Perdiguer, Nuria Carreras, Caldes de Montbui, Spain
PA Laboratorios Cusi, S.A., Barcelona, Spain (non-U.S. corporation)
PI US 5698219 19971216
AI US 1995-509746 19950731 (8)
PRAI ES 1994-1784 19940808
DT Utility
LN.CNT 779
INCL INCLM: 424/450.000
INCLS: 436/829.000; 514/912.000
NCL NCLM: 424/450.000

NCLS: 436/829.000; 514/912.000
IC [6]
ICM: A61K009-127
EXF 424/450; 436/829; 514/912
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 4 OF 10 USPATFULL
AN 97:83632 USPATFULL
TI Topical preparation containing a suspension of solid lipid particles
IN De Vringer, Tom, Zoetermeer, Netherlands
PA Yamanouchi Europe B.V., Netherlands (non-U.S. corporation)
PI US 5667800 19970916
AI US 1995-467212 19950606 (8)
RLI Division of Ser. No. US 1993-131480, filed on 4 Oct 1993, now abandoned
And a continuation of Ser. No. US 1992-857467, filed on 25 Mar 1992, now abandoned
PRAI EP 1995-91200664 19950325
DT Utility
LN.CNT 785
INCL INCLM: 424/450.000
INCLS: 424/078.020; 424/078.030
NCL NCLM: 424/450.000
NCLS: 424/078.020; 424/078.030
IC [6]
ICM: A61K009-127
EXF 424/78.02; 424/78.03; 424/450
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 5 OF 10 USPATFULL
AN 96:94322 USPATFULL
TI Polyalkylene block copolymers as surface modifiers for **nanoparticles**
IN Wong, Sui-Ming, Collegeville, PA, United States
Cooper, Eugene R., Berwyn, PA, United States
Xu, Shugian, Exton, PA, United States
PA NanoSystems L.L.C., Collegeville, PA, United States (U.S. corporation)
PI US 5565188 19961015
AI US 1995-393972 19950224 (8)
DT Utility
LN.CNT 952
INCL INCLM: 424/009.411
INCLS: 424/009.400; 424/009.450; 424/489.000; 424/495.000; 424/499.000; 514/718.000; 514/975.000
NCL NCLM: 424/009.411
NCLS: 424/009.400; 424/009.450; 424/489.000; 424/495.000; 424/499.000; 514/718.000; 514/975.000
IC [6]
ICM: A61K009-14
EXF 424/489; 424/495; 424/499; 424/4; 424/5; 514/718; 514/975
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 6 OF 10 USPATFULL
AN 96:19084 USPATFULL
TI Submicron **emulsions** as ocular drug delivery vehicles
IN Aviv, Haim, Rehovot, Israel
Friedman, Doron, Carmei Yossef, Israel
Bar-Ilan, Amir, Neve Monsson, Israel
Vered, Micha, Rehovot, Israel
PA Pharmos Corp., New York, NY, United States (U.S. corporation)
PI US 5496811 19960305
AI US 1993-854 19930105 (8)
PRAI IL 1992-102984 19920828
IL 1992-103907 19921127
DT Utility
LN.CNT 842
INCL INCLM: 514/078.000

INCLS: 514/075.000; 514/076.000; 514/546.000; 514/547.000; 514/560.000; 514/912.000
NCL NCLM: 514/078.000
NCLS: 514/075.000; 514/076.000; 514/546.000; 514/547.000; 514/560.000; 514/912.000
IC [6]
ICM: A61K031-685
ICS: A61K031-66; A61K031-22; A61K031-225
EXF 514/76; 514/75; 514/78; 514/912; 514/546; 514/547; 514/560
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 7 OF 10 USPATFULL
AN 95:36490 USPATFULL
TI Photopolymerizable biodegradable hydrogels as tissue contacting materials and controlled-release carriers
IN Hubbell, Jeffrey A., Austin, TX, United States
Pathak, Chandrashekhar P., Waltham, MA, United States
Sawhney, Amarpreet S., Newton, MA, United States
Desai, Neil P., Los Angeles, CA, United States
Hill, Jennifer L., Austin, TX, United States
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
PI US 5410016 19950425
AI US 1993-22687 19930301 (8)
RLI Continuation-in-part of Ser. No. US 1992-843485, filed on 28 Feb 1992, now abandoned Ser. No. Ser. No. US 1990-598880, filed on 15 Oct 1990
And
Ser. No. US 1991-740703, filed on 5 Aug 1991 which is a division of Ser.
No. US 19 -598880
DT Utility
LN.CNT 2205
INCL INCLM: 528/354.000
INCLS: 128/898.000; 424/426.000; 424/489.000; 525/054.100; 525/054.200; 525/408.000; 525/413.000; 525/415.000; 514/772.100; 514/772.300; 514/773.000; 514/777.000; 528/361.000
NCL NCLM: 528/354.000
NCLS: 128/898.000; 424/426.000; 424/489.000; 514/772.100; 514/772.300; 514/773.000; 514/777.000; 522/014.000; 522/026.000; 522/044.000; 522/048.000; 522/088.000; 522/181.000; 525/054.100; 525/054.200; 525/408.000; 525/413.000; 525/415.000; 528/361.000
IC [6]
ICM: C08G063-08
ICS: C08G067-00; A61K009-58
EXF 424/426; 424/489; 514/772.1; 514/772.3; 514/773; 514/777; 525/54.1; 525/54.2; 525/408; 525/413; 525/415; 528/354; 528/361; 128/898
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L21 ANSWER 8 OF 10 CAPLUS COPYRIGHT 1999 ACS
AN 1999:736228 CAPLUS
TI Use of **nanodispersions** in pharmaceutical compositions
IN Supersaxo, Andreas Werner; Weder, Hans Georg; Hueglin, Dietmar; Roeding, Joachim Friedrich
PA Ciba Specialty Chemicals Holding Inc., Switz.; Vesifact A.-G.
SO Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 956853	A2	19991117	EP 1999-810383	19990504
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	EP 1998-810422		19980511		

L21 ANSWER 9 OF 10 CAPLUS COPYRIGHT 1999 ACS
AN 1999:565967 CAPLUS
DN 131:186960
TI Methods for the preparation of **nanoparticles** of metals and oxides
IN Garti, Nissim; Berkovich, Yana
PA Yissum Research Development Company of the Hebrew University of Jerusalem, Israel
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9943427	A1	19990902	WO 1999-IL97	19990216

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI IL 1998-123468 19980226

L21 ANSWER 10 OF 10 CAPLUS COPYRIGHT 1999 ACS
AN 1998:473949 CAPLUS
DN 129:140450
TI Cosmetic **nanodispersion**
IN Weder, Hans Georg; Weder, Marc Antoine
PA Vesifact A.-G., Switz.
SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 852941	A1	19980715	EP 1997-810951	19971205

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI CH 1996-3065 19961213
OS MARPAT 129:140450

=> d kwic 2 3 6 8 9 10

L21 ANSWER 2 OF 10 USPATFULL
SUMM . . . Numerous publications propose the encapsulation of sparingly soluble therapeutic agents in micelles, mixed micelles, inverse micelles or unilamellar or multilamellar **liposomes**.
SUMM In an especially preferred embodiment of the process, an intravenously administrable dispersion having **nanoparticles** of the sparingly water-soluble staurosporin derivative N-benzoyl-staurosporin is prepared.
SUMM . . . forms in which the solubilisation of a sparingly soluble active ingredient is necessary, for example capsule fillings, drops, lotions or **emulsions** for ointments, gels, creams etc. To the latter there may also be added the other excipients typical of such dosage. . .

SUMM In accordance with an especially preferred process variant, an intravenously administrable dispersion containing **nanoparticles** of the sparingly water-soluble staurosporin derivative N-benzoyl-staurosporin and having the following formulation base is prepared:

SUMM The mixture obtainable can be defined as a suspension of colloidal **nanoparticles** of the sparingly soluble staurosporin derivative or, more simply, as a nanosuspension. By means of measurements from laser light scattering. . . colloidal particles present in the suspension can be distinguished from other particles such as liquid crystals, micelles, inverse micelles or **liposomes**. For the statistical plurality of more than 90%, especially more than 95%, an average particle size of less than 20. . .

DETD . . . at 35.degree. C. The glycerol is then mixed in and stirring is continued at room temperature until the mixture becomes **clear**. The 70% sorbitol **solution**, which has been prepared beforehand by dissolving sorbitol in water, is then added. The mixture is again stirred using the magnetic stirrer until the mixture becomes **clear**. The **mixture** is then sterile-filtered (pore filter: 0.2 .mu.m) and introduced into containers under sterile conditions. The formulations are then stored at. . .

CLM What is claimed is:

7. A process according to claim 6, which comprises preparing an intravenously administrable dispersion containing **nanoparticles** of the sparingly water-soluble staurosporin derivative N-benzoyl-staurosporin.

IT **106392-12-5**, Polyoxyethylene-polyoxypropylene block copolymer (nanosuspensions of N-benzoylstaurosporine for i.v. application)

L21 ANSWER 3 OF 10 USPATFULL

SUMM . . . in the field of the release of drugs, specifically for use in Ophthalmology, by means of oil in water type **emulsion**. The present invention provides a vehicle that produces an increase of the corneal penetration of the active substance included in. . .

SUMM Likewise, a large number of novel vehicles have been developed such as **liposomes**, **nanoparticles**, etc., though most of them have problems of stability, tolerance, difficulties for industrialization thereof and even relative success as far. . .

SUMM Different types of **emulsions** have been suggested as vehicles for the release of drugs at the eye level.

SUMM Among these, patent application EP 0 521 799 A1 describes an oil in water type **emulsion** for the release of hydrophobic, amphiphilic and lipophilic drugs. Its composition comprises an oil, phospholipids and an amphoteric surface active agent. Although the role of phospholipids is essential for the stability of the **emulsions** of said invention, possible cataractogenic effects due to the phosphatidyl choline and, basically, to a derivative of the same, lysophosphatidyl,. . .

SUMM U.S. Pat. No. 5,171,566 describes an oil in water type **emulsion**, that comprises a soybean oil and soybean lecithin as an emulsifier. This type of **emulsion**, upon including lecithins, also contain phosphatidyl choline for which reason they may have the same problems of toxicity mentioned above. Likewise, they contain other stabilizers such as cholesterol or phosphatidic acid. This **emulsion** is lyophilized or it is to be kept at 4.degree. C. This composition has the same inconveniences as the above. . .

SUMM Patent application EP 0 480 690 A1, though it describes an **emulsion** type ophthalmic product, deals with a product that is substantially different from the object of the present invention. Said application claims the preparation of a **microemulsion** of tepoxaline whose aspect is that of a translucent to **transparent** formulation, inherent characteristic of **microemulsions** with a drop size of 0.005 to 0.5 .mu.m. For the preparation of the same the use

of sonification is. . . the preservative(s) is from 0.02 to 0.7% (w/v). The present invention deals with a different composition since instead of a **microemulsion** it is a nanoemulsion neither **transparent** nor translucent (transmittance at 520 nm lower than 70%.) Likewise, the amount of preservative used is much less than that. . .

SUMM The present invention provides an oil in water type **emulsion** type preparation that increases the bioavailability in the eye of the drug in the vehicle. Said **emulsion** is stable during storage without the need of including in its composition potentially irritating products and ones that can cause. . . such as those mentioned above, do not meet the requirements of pharmacopeia for ophthalmic products. On the other hand, the **emulsions** of the present invention can be obtained with normal emulsification equipment, with a rotary agitator or else with a pressurized. . .

SUMM . . . with the present invention, the oil soluble or partly oil soluble drugs are included in an oil in water type **emulsion** to be administered in the eye thus increasing the bioavailability of the same with regard to other compositions. Said vehicle. . .

SUMM The oil that forms part of the **emulsion** may be a vegetable oil, an animal oil, a mineral oil, fatty acids, a medium chain triglyceride, fatty alcohols or. . .

SUMM The **emulsion** of the present invention shows a transmittance measured at 520 nm less than 70%, a pH between 5 and 8 and an osmolality between 250 and 400 mOsm/kg. The appearance of these **emulsions** tends to be light milky.

SUMM For the preparation of the **emulsion** the oily phase is added to the aqueous phase under moderate agitation and subsequently the particle size is reduced by. . .

SUMM Another particular preparation method of the present invention allows an oil in water type **emulsion** to be obtained with average size droplets of 200 nm at a temperature no higher than 35.degree. C., unlike the. . .

SUMM . . . by a suitable evaporation system and at a temperature no higher than 35.degree. C., obtaining a very fine and homogenous **emulsion.**

DRWD FIG. 1 is a graph that represents the study of the stability of **Emulsion** A in contrast to time, showing the results of the average size of the droplets in nm.

DRWD FIG. 2 is a graph that represents the study of the stability of **Emulsion** B in contrast to time, showing the results of the average size of the droplets in nm.

DRWD FIG. 3 is a graph that represents the study of the polydispersity of **Emulsion** A in contrast to time.

DRWD FIG. 4 is a graph that represents the study of the polydispersity of **Emulsion** B in contrast to time.

DRWD FIG. 5 is a graph that represents the study of the pH of **Emulsion** A incontrast to time.

DRWD FIG. 6 is a graph that represents the study of the pH of **Emulsion** B in contrast to time.

DRWD FIG. 7 is a graph that represents the study of the stability of **Emulsion** C in contrast to time, showing the results of the average size of the droplets in nm.

DRWD FIG. 8 is a graph that represents the study of the polydispersity of **Emulsion** C in contrast to time.

DRWD FIG. 9 is a graph that represents the study of the pH of **Emulsion** C in contrast to time.

DRWD FIG. 10 is a graph that represents the study of the evolution of the content of active principle of **Emulsion** C in contrast to time,

in percentage with regard to the initial theoretical content.

DETD In all the formulations that are described hereinafter, the two phases are either sterilized separately and the **emulsion** is prepared aseptically or the final product is sterilized by 0.22 .mu.m filter filtration.

DETD NANOEMULSION OF MIGLYOL 812.RTM. (**EMULSION** A)

DETD . . . edetate (stabilizer), 27.4 g. of sorbitol powder (isotonizing agent) and 0.05 g of benzalkonium chloride (preservative) are added to this **emulsion**. The resulting concentrations are:

DETD NANOEMULSION OF MIGLYOL 812.RTM. (**EMULSION** B)

DETD NANOEMULSION OF CARTEOLOL BASE 0.2% (**EMULSION** C)

DETD . . . neutralized up to a pH=7.4, with a 0.1N HCl solution 10.14 g. of apyrogenic mannitol are added to the previous **emulsion** to isotonize it and then 2 ml. of a benzalkonium chloride solution 1% (w/v) are added. Finally, the volume is. . .

DETD NANOEMULSION OF INDOMETHACIN 0.1% (**EMULSION** D)

DETD GEL WITH A NANOEMULSION OF MYGLYOL 812.RTM. (**EMULSION** E)

DETD . . . 0.5 .mu.m. 1.014 g. of apyrogenic mannitol and 0.2 ml. of benzalkonium chloride solution 1% (w/v) are added to this **emulsion**. To complete the formula, 5 g. of Carbol 940 gel 0.6%, previously prepared, are added. It is stirred with a. . .

DETD NANOEMULSION OF MIGLYOL 812.RTM. (**EMULSION** F)

DETD . . . dispersion is passed through the Ultra-turrax homogenizer (Janke and Kunkel, Staufen, Germany) for 15 minutes at 10,000 r.p.m. until an **emulsion** with a size smaller than 0.5 .mu.m is obtained. Then, 10.96 g. of sorbitol powder, 0.10 g. of disodium edetate. . .

DETD NANOEMULSION OF MIGLYOL 812.RTM. (**EMULSION** G)

DETD . . . dispersion is passed through the Ultra-turrax homogenizer (Janke and Kunkel, Staufen, Germany) for 10 minutes at 10,000 r.p.m. until an **emulsion** with a size smaller than 0.5 .mu.m is obtained. Then, 5.48 g. of sorbitol powder and 1 ml. of a. . .

DETD The stability of **emulsion** A and of **emulsion** B kept at different temperatures has been followed up. Controls have been carried out at different time periods and the. . .

DETD The acute eye tolerance of **emulsion** B and of **emulsion** D was evaluated in New Zealand albino rabbits by means of repeated instillation of 50 .mu.l every 20 minutes for. . .

DETD The results obtained indicate that **emulsion** B as well as **emulsion** D have a correct eye irritation index.

DETD . . . the most important pharmacopoeia with a concentration of preservative much lower than that used in other oil in water type **emulsions**, which do not meet the requirements of pharmacopoeia with regard to preservative effectiveness using the concentrations of preservatives used in. . .

DETD TABLE 1

EMULSION F

Inoculum ufc/ml

Colony forming units-time after inoculation

Microorganism

0 hours 0 hours

6 hours

24 hours

7 days

14 days

. . .

DETD TABLE 2

EMULSION A

Inoculum ufc/ml

Colony forming units-time after inoculation

Microorganism

0 0 hours

6 hours

24 hours
7 days
14 days
28. . .

DETD TABLE 3

EMULSION G

Inoculum ufc/ml
Colony forming units-time after inoculation
Microorganism
0 0 hours
6 hours
24 hours
7 days
14 days
28. . .

CLM What is claimed is:
1. A nanoemulsion comprised of droplets having oil cores, useful as an ophthalmic vehicle, obtained by preparing an **emulsion** of an aqueous phase in an oil phase, said oil phase comprising an oil in an amount of 0.1-10% in. . .

IT 50-02-2, Dexamethasone 50-70-4, Sorbitol, biological studies 50-99-7, Glucose, biological studies 53-86-1, Indomethacin 56-81-5, Glycerol, biological studies 69-65-8, Mannitol 77-92-9, Citric acid, biological studies 139-33-3 144-55-8, Sodium bicarbonate, biological studies 497-19-8, Sodium carbonate, biological studies 994-36-5, Sodium citrate 7558-79-4, Disodium phosphate 7778-77-0, Monopotassium phosphate 9003-01-4D, Polyacrylic acid, derivs. 9003-11-6, Polyoxyethylene-polyoxypropylene copolymer 9004-32-4, Sodium cm cellulose 9004-65-3, Hydroxypropylmethyl cellulose 15307-86-5, Dichlofenac 15687-27-1, Ibuprofen 29122-68-7, Atenolol 36322-90-4, Pyroxycam 51781-06-7, Carteolol 54063-32-0, Clobetasone 59277-89-3, Acyclovir 59865-13-3, Cyclosporin a 63659-18-7, Betaxolol 76050-42-5, Carbopol 940 **106392-12-5**, Lutrol f68
(ophthalmic vehicle emulsions and process for their prepn.)

L21 ANSWER 6 OF 10 USPATFULL

TI Submicron **emulsions** as ocular drug delivery vehicles

AB An ocular drug delivery vehicle of an oil-in-water submicron **emulsion** comprising about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a second component. . .

SUMM . . . agents to a patient through the eye by application of the innovative compositions of these agents in a non-irritating submicron **emulsion**.

SUMM . . . which also enable delivery of hydrophobic drugs into the eye. Additionally, many attempts to use various non-conventional carriers, such as **liposomes**, micellar solutions and **nanoparticles**, as vehicles of ophthalmic drugs have also been made. While the use of such delivery systems may provide limited success. . .

SUMM **Emulsions** have also been suggested as vehicles for delivery of drugs to the eye in references such as EP 391,369, Ellis. . . J. Ocular Pharmcol. (U.S.) 3:121-128, and Shell (1984) Surv. Ophthalmol. 29:177-178. Nevertheless, the practical inability to realize the potential of **emulsion** systems for ocular drug delivery stems predominantly from two problems. First, ocular drug formulations must be comfortable to the patient as well as safe, due to the sensitivity of the delicate eye tissues involved. Second, **emulsions** are generally metastable dispersions of immiscible fluids and these instability problems must be overcome.

SUMM An **emulsion** is a dispersion of oil in water ("o/w"), and can

be defined as either a macroemulsion or a **microemulsion**. A macroemulsion is a cloudy turbid composition having an oil-droplet size of 0.5 to 100 .mu.m and is generally thermodynamically unstable. In comparison, a **microemulsion** is a translucent to **transparent** composition having a droplet size of 0.005 to 0.5 .mu.m, is thermodynamically stable and is generally self emulsifying. See, e.g., Friberg et al. (1987) **Microemulsions** Structure and Dynamics, CRC Press Inc., Boca Raton, Fla., pp. 154. Also, the proportion of surfactants to oil required to generate **microemulsions** is generally much higher than in macroemulsions.

SUMM **Emulsions** developed specifically for ophthalmic use have attempted to solve the problem of inherent instability through the use of **microemulsions** or the addition of stabilizing polymers to classical **emulsions**. In several instances, specific drugs have been formulated successfully in **microemulsions**. Examples of this approach include ophthalmic **microemulsions** of tepoxalin, as disclosed in EP 480,690, or flurbiprofen, as disclosed in EP 253,472.

SUMM An alternative approach to solve the problem of **emulsion** instability utilizes lightly crosslinked polymers, as exemplified by the autoclavable **emulsions** for ophthalmic use which are disclosed in EP 028,110.

SUMM In addition, the use of **emulsions** in ophthalmic preparations has been limited to a large extent by the inclusion of surfactants in the **emulsions** which surfactants are highly irritating to the eye. For example, the use of the **emulsion** preparations of EP 391,369 are limited considerably by the irritating effect of the ionic surfactants which are used in those **emulsions**. Thus, to date no commercially successful ophthalmic compositions in the form of oil-in-water **emulsions** are available.

SUMM The present invention solves the problem of **emulsion** instability without resorting to either of the prior art suggestions by instead converting classical **emulsions** to submicron **emulsions** with the input of energy by shear forces and homogenization to provide submicron **emulsions** possessing substantially reduced eye irritation properties. Also, the irritation of the eye is further reduced through the use of non-irritating non-ionic surfactants in such **emulsions**. Thus, when drugs are included with these submicron **emulsions**, the present invention provides ophthalmic compositions which are improved over those which are currently available in the art. In accordance. . .

SUMM The present invention provides an ocular drug delivery vehicle of an oil-in-water submicron **emulsion** comprising about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a second component. . .

SUMM . . . present invention also provides a method for reducing eye irritation which comprises topically administering to the eye the oil-in-water submicron **emulsion** described above. A particular aspect of this embodiment of the present invention is the combined topical administration to the eye of the submicron **emulsion** defined above and an effective amount of a drug, in order to reduce irritation which may otherwise be induced by. . .

DRWD . . . 1 shows the baseline intraocular pressure ("IOP") in eyes of rabbits and the IOP following administration of a pilocarpine containing **emulsion** which includes the non-ionic surfactant TYLOXAPOL;

DRWD FIG. 2 shows the IOP results from the contralateral eyes of the rabbits which received the pilocarpine **emulsion** as per FIG. 1;

DRWD FIG. 3 shows miosis in an eye of human subjects following treatment with a 2% pilocarpine **emulsion** composition compared to the same **emulsion** without pilocarpine;

DRWD FIG. 4 shows miosis in the contralateral eye of human subjects following

treatment with a 2% pilocarpine **emulsion** composition compared to the same **emulsion** without pilocarpine, as per FIG. 3;

DRWD FIG. 5 shows the IOP in human subjects following administration of a 2% pilocarpine containing **emulsion** versus baseline in both treated and contralateral eyes with a comparison to the administration of the same **emulsion** without pilocarpine; and

DRWD FIG. 6 shows the change in IOP versus baseline level in human subjects following administration of a 2% pilocarpine containing **emulsion** versus for both treated and contralateral eyes with a comparison to the administration of the same **emulsion** without pilocarpine.

DETD The present invention has for the first time achieved **emulsions** effective as a general drug delivery vehicle for ophthalmological use. The present invention provides stable pharmaceutical preparations which are oil-in-water **emulsions** having droplets or colloidal particles of a submicron size and utilizing surfactants that are non-ionic.

DETD . . . ophthalmic drugs, while simultaneously providing enhanced bioavailability of certain drugs. In parallel, the intrinsic problems of instability of drug containing **emulsions** have been solved by providing the droplet size of the oil phase in the submicron range.

DETD . . . to mean a size of about 0.05 to 0.5 .mu.m, and preferably about 0.1 to 0.3 .mu.m. Thus, a submicron **emulsion** having droplets of these sizes would be smaller than those of a classical macroemulsion, which has droplet sizes of above 0.5 .mu.m, but generally larger than those of a classical **microemulsion**, which, for practical purposes, has droplet sizes of less than 0.1 .mu.m.

DETD These submicron **emulsion** can easily be sterilized by filtration, for example, in 0.45 .mu.m and/or 0.22 .mu.m filters, are more stable in long-term. . .

DETD An oil-in-water **emulsion** is a dispersion of droplets or colloidal particles in an aqueous medium, with the colloid particles having an oily core. . .

DETD . . . oil, it is separately identified herein because of its particular utility as a preferred oil for use in the present **emulsions**. In addition, MCT oil is available commercially. Examples of such MCT oils include TCR (trade name of Societe Industrielle des. . .

DETD The aqueous component will be the continuous phase of the **emulsion** and may be water, saline or any other suitable aqueous solution which can yield an isotonic and pH controlled preparation.

DETD The **emulsion** used in the ophthalmic compositions of the present invention may comprise about 0.5 to 50% oil, about 0.1 to 10%. . .

DETD The present invention is also based on the surprising finding that the colloidal particles of the oil-in-water **emulsions** disclosed herein have a soothing and irritation reducing effect on the eye. Thus, where a drug which otherwise causes an. . . have otherwise occurred, is reduced considerably. The soothing effect of the composition of the present invention also occurs where an **emulsion** without a drug is administered to an already irritated eye. Thus, the submicron **emulsions** of the present invention are useful for reducing drug-induced irritation of a number of pharmaceuticals.

DETD Example 1: A blank oil-in-water type **emulsion** (without a drug) was prepared from the following ingredients:

DETD The **emulsion** was prepared as follows:

DETD . . . heated separately to over 50.degree. C. and then were combined and stirred with a magnetic stirrer to produce a coarse **emulsion**. The mixture was further heated to a temperature of 80.degree.-85.degree. C. The coarse **emulsion** was further mixed by a high-shear mixer, POLYTRON (Kinematica, Switzerland), for 3 minutes, and then was rapidly cooled to below 40.degree. C. After cooling, the **emulsion** was homogenized by a 2-stage homogenizer (APV Montin Gaulin, Germany) at 8000 psi and then cooled again to

storage (i.e., room) temperature. After adjusting the pH to 6.8-7, the **emulsion** was filtered through a membrane filter (TE, Schleicher & Schull, having a pore size of 0.45 .mu.m) and transferred to plastic bottles that were sealed under nitrogen atmosphere. The **emulsions** were then sterilized either by a steam autoclave at 121.degree. C. or by a double stage membrane filtration, through a. . .

DETD

. . . 1.5 .+-. 0.4

1.6 .+-. 0.4

1.6 .+-. 1.2

1.5 .+-. 0.3

(Betoptic)

Means .+-. S.D. (n = 10 animals)

*Submicron **emulsion** significantly differs from aqueous solution at P < 0.05.

DETD TABLE 2

Long Term Irritative Response

	Irritative index No. of treatment (drops)				
Treatment	2	6	9	13	18
Emulsion alone	1.0 .+-. 0.8				
		0.2 .+-. 0.2			
			0.4 .+-. 0.3		
				0.2 .+-. 0.2	
					0.9 .+-. 0.5
Adaprolol 0.4%	3.0 .+-. 0.9				
. . .	0.8				
					3.6 .+-. 0.7
(aqueous sol.)					
Adaprolol 0.4%	1.5 .+-. 1.0*				
		2.0 .+-. 1.0			
			1.7 .+-. 0.6*		
				1.8 .+-. 0.7*	
					2.7 .+-. 1.5*
Emulsion Timoptic	1.4 .+-. 0.9				
		2.3 .+-. 0.8			
			0.9 .+-. 0.2		
				2.3 .+-. 0.9	
					1.1 .+-. 0.7
0.5% Timolol Maleate					
Timolol Maleate	0.6 .+-. 0.4*				
		1.1 .+-. 0.7*			
			1.0 .+-. 1.0		
				1.4 .+-. 1.2*	
					0.7 .+-. 0.8*
0.5% **Emulsion**					

Means .+-. S.D. n = 12 eyes

*Submicron **emulsion** formulations significantly differ at P < 0.05 from buffer/aqueous formulation

DETD These results clearly show that drugs administered with the submicron **emulsion** formulations of the present invention were much less irritating than drugs administered in standard formulations, whether the

drug is hydrophilic. . .

DETD . . . were found to be acceptable. The phospholipid oxidation was less than 0.3% measured by the tetrabarbituric acid method described in **Liposome** Technology, 2nd edition (1992) Gregoriadis, ed., CRS Press Inc., Boca Raton, Fla. pp 501-527.

DETD . . . of Example 7, the pH dropped from 6 to 5.4 which is reasonable under these conditions. Visual observations of the **emulsion** properties were acceptable, and there was only minor phospholipid oxidation.

DETD . . . administered in either a generic composition (comprising pilocarpine hydrochloride in aqueous buffer at about pH 5) or with the TYLOXOPOL **emulsion** of Example 2. The compositions were administered to the right eye of the rabbits following three days' measurement of baseline. . .

DETD As can be seen in FIG. 1, a single dose of the TYLOXAPOL **emulsion** of Example 2 caused a decrease in IOP levels which persisted throughout the entire tested period. The maximal change in IOP

reduction obtained by a single dose of this **emulsion** was 16% and was noted at 24 and 34 hours after administration.

DETD A study on the clinical affects of the 2% pilocarpine **emulsion** of Example 2 was made. The study was performed on 20 young healthy volunteers, each receiving a single topical dose in the right eye of either the 2% pilocarpine **microemulsion** or of a placebo containing the **microemulsion** alone. The parameters that were measured in each case were IOP and a decrease of the pupil diameter (miosis).

DETD . . . also in the untreated (left eye) which likely occurs as a result of a systemic reaction. As a control, the **emulsion** of Example 1 was administered in a similar manner, and no significant change in IOP was measured.

CLM What is claimed is:

1. An ocular drug delivery vehicle of an oil-in-water submicron **emulsion** consisting essentially of about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a. . . of an emulsifier, comprising a phospholipid, about 0.05 to 5% of a non-ionic surfactant and an aqueous component, said submicron **emulsion** having a mean droplet size in the range of 0.05 to 0.5 .mu.m, and a weight ratio of surfactant to. . .

. . . of an emulsifier, comprising a phospholipid, about 0.05 to 5% of a non-ionic surfactant and an aqueous component, said submicron **emulsion** having a mean droplet size in the range of 0.05 to 0.5 .mu.m, and a weight ratio of surfactant to. . .

24. The method of claim 23 which further comprises selecting the **emulsion** to have droplets of a mean diameter of between about 0.1 and 0.3 .mu.m.

26. The method of claim 25 which further comprises selecting the **emulsion** to have droplets of a mean diameter of between about 0.1 and 0.3 .mu.m.

28. The method of claim 27 which further comprises selecting the **emulsion** to have droplets of a mean diameter of between about 0.1 and 0.3 .mu.m.

30. The method of claim 29 which further comprises selecting the **emulsion** to have droplets of a mean diameter of between about 0.1 and 0.3 .mu.m.

32. The method of claim 31 which further comprises selecting the **emulsion** to have droplets of a mean diameter of between about 0.1 and 0.3 .mu.m.

34. The method of claim 33 which further comprises selecting the **emulsion** to have droplets of a mean diameter of between about 0.1 and 0.3 .mu.m.

36. The method of claim 35 which further comprises selecting the **emulsion** to have droplets of a mean diameter of between about 0.1 and 0.3 .mu.m.

IT **9005-65-6**, Tween 80 25301-02-4, Tyloxapol
(ocular drug delivery vehicles contg.)

L21 ANSWER 8 OF 10 CAPLUS COPYRIGHT 1999 ACS
TI Use of **nanodispersions** in pharmaceutical compositions
AB **Nanodispersions** contg. a membrane-forming mol. (e.g. a phospholipid or ceramide), an oil-in-water coemulsifier, and a lipophilic component are useful as drug delivery vehicles. The **nanodispersions** are prepd. by mixing these 3 components to form a **homogeneous clear** liq., and adding this liq. to an aq. phase at room temp., which approximates the phase inversion temp.; the **nanodispersion** (mean particle size <50 nm) forms with no further energy expenditure for homogenization, sonication, etc. Thus, vitamin A palmitate 4.50,. . . parts were combined and mixed with a soln. of soybean lecithin 17.30 in EtOH 14.20 wt. parts to produce a **homogeneous clear** liq. This liq. was mixed 1:9 with 10 mM phosphate buffer (pH 7.4) at 50.degree. with stirring to produce a **nanodispersion**.
ST pharmaceutical **nanodispersion** phospholipid emulsifier; vitamin A **nanodispersion** phospholipid emulsifier; dispersion vitamin A phospholipid emulsifier
IT Alcohols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C2-8; use of **nanodispersions** in pharmaceutical compns.)
IT Glycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10; use of **nanodispersions** in pharmaceutical compns.)
IT Betaines
Sulfobetaines
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-18, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Fatty acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-20, salts, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Sulfonates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkanesulfonates, C8-20, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Glycosides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkyl, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Phenols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkyl, ethoxylated, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(capsules; use of **nanodispersions** in pharmaceutical compns.)
IT Bile salts
Glycerides
Proteins, general
Quaternary ammonium compounds
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Mineral elements
Vitamins
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(deficiency disorders; use of **nanodispersions** in pharmaceutical compns.)
IT Endocrine system
Mucous membrane
Nervous system
Respiratory tract
Urinary tract
(disease; use of **nanodispersions** in pharmaceutical compns.)
IT Immunity
(disorder; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(drops; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(**emulsions**; use of **nanodispersions** in pharmaceutical compns.)
IT Lanolin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated, coemulsifier; use of **nanodispersions** in pharmaceutical compns.)
IT Carbohydrates
Fatty acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Blood
(ext. of, Solcoseryl; use of **nanodispersions** in pharmaceutical compns.)
IT Amides
Amines
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fatty, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Alcohols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fatty, ethoxylated, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Alcohols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fatty; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(freeze-dried; use of **nanodispersions** in pharmaceutical compns.)
IT Drugs
(gastrointestinal; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(granules; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(hydrogels; use of **nanodispersions** in pharmaceutical compns.)
IT Peanut oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(implants; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(infusions; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(inhalants; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(injections; use of **nanodispersions** in pharmaceutical compns.)
IT Alcohols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lanolin; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems

(liqs., dispersions, **nanodispersions**; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(liqs.; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(lotions; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(lozenges; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(**microcapsules**; use of **nanodispersions** in pharmaceutical compns.)
IT Esters
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(of Guerbet alcs.; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(ointments, creams; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(ointments; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(ophthalmic; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(pastes; use of **nanodispersions** in pharmaceutical compns.)
IT Medical goods
(plasters; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(powders; use of **nanodispersions** in pharmaceutical compns.)
IT Lecithins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soya; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(sprays; use of **nanodispersions** in pharmaceutical compns.)
IT Carbohydrates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sugar esters, with fatty acids, coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(suspensions; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(tablets, chewable; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(tablets, effervescent; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(tablets; use of **nanodispersions** in pharmaceutical compns.)
IT Drug delivery systems
(transdermal; use of **nanodispersions** in pharmaceutical compns.)
IT Anti-infective agents
Anti-inflammatory agents
Antioxidants
Antitumor agents
Cardiovascular agents
Emulsifying agents
Kidney, disease
Mouthwashes
Musculoskeletal diseases
Skin, disease
(use of **nanodispersions** in pharmaceutical compns.)
IT Ceramides
Lipids
Lysophospholipids

Paraffin oils
Phospholipids
Polysiloxanes
Waxes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **nanodispersions** in pharmaceutical compns.)

IT 36653-82-4, Cetyl alcohol **106392-12-5**, ethylene oxide/propylene oxide block copolymer
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coemulsifier; use of **nanodispersions** in pharmaceutical compns.)

IT 50-21-5D, Lactic acid, esters with fatty acids 57-55-6D, Propylene glycol, esters with fatty acids 1406-18-4D, vitamin E, ethoxylated derivs. 7664-38-2D, Phosphoric acid, alkyl esters 7664-93-9D, Sulfuric acid, alkyl and alkenyl esters 12441-09-7D, Sorbitan, esters with fatty acids 25322-68-3D, PEG, derivs. 25618-55-7D, Polyglycerol, esters with fatty acids 31694-55-0D, triesters with fatty acids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coemulsifiers; use of **nanodispersions** in pharmaceutical compns.)

IT 58-95-7, vitamin E acetate 79-81-2, vitamin A palmitate 81-13-0, Dexpanthenol 19666-16-1 249747-47-5
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **nanodispersions** in pharmaceutical compns.)

IT 57-55-6, Propylene glycol 3687-45-4, Oleyl oleate **9004-98-2**, Oleth **9005-65-6**, Polysorbate 80 9005-67-8, Polysorbate 60
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **nanodispersions** in pharmaceutical compns.)

L21 ANSWER 9 OF 10 CAPLUS COPYRIGHT 1999 ACS

TI Methods for the preparation of **nanoparticles** of metals and oxides

AB **Nanoparticles** (1-6 nm) of transition metals (e.g., Pt, Pd), alloys, metal oxides (e.g., FeOOH, SiO2), and ceramics are prepd. by chem. reaction under mild conditions using precursor solns. of complex liqs. (e.g., **microemulsions**, liq. crystals) contg. surfactants and alkoxides. The resulting **nanoparticles** are dispersed in polymer solns. as fine colloids, and used to form **transparent nanoparticle**-contg. plastic films. The water is non freezing, the mild conditions are atm. pressure and a temp. range of room temp.. . . 75.degree.C for 1 h. The solvent was evapd. off, leaving a waxy residue which was washed and dried. The Pd **nanoparticles** were redispersed in polyvinylalc., and used for forming a **transparent** film coating on a glass plate.

ST **nanoparticle** prodn chem reaction complex liq; oxide
nanoparticle prodn chem reaction complex liq; metal
nanoparticle prodn chem reaction complex liq; ceramic
nanoparticle prodn chem reaction complex liq; plastic film
dispersed **nanoparticle** prodn

IT Plastic films
(**nanoparticles** in; prodn. of nanosized particles of metals and oxides by hydrolysis, redn. or ion exchange)

IT Alloys, preparation
Oxides (inorganic), preparation
Platinum-group metals
Transition metals, preparation
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PREP (Preparation); PROC (Process)
(**nanoparticles**; prodn. of nanosized particles of metals and oxides by hydrolysis, redn. or ion exchange)

IT Ceramic powders
Hydrolysis

Ion exchange
Nanoparticles
Powders
Reduction
Solvents
Surfactants
(prodn. of nanosized particles of metals and oxides by hydrolysis, redn. or ion exchange)

IT 7440-05-3P, Palladium, preparation 7440-06-4P, Platinum, preparation 7631-86-9P, Silica, preparation 11115-92-7P, Iron hydroxide oxide
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PREP (Preparation); PROC (Process)
(**nanoparticles**; prodn. of nanosized particles of metals and oxides by hydrolysis, redn. or ion exchange)

IT 112-02-7, Cetyltrimethylammonium chloride 577-11-7, Sodium bis(2-ethylhexyl)sulfosuccinate 5137-55-3, Trioctylmethylammonium chloride 5538-94-3, Dioctyldimethylammonium chloride **9004-98-2**, Polyethylene oxide, oleyl ether
RL: NUU (Nonbiological use, unclassified); USES (Uses)
(surfactants; prodn. of nanosized particles of metals and oxides by hydrolysis, redn. or ion exchange)

L21 ANSWER 10 OF 10 CAPLUS COPYRIGHT 1999 ACS

TI Cosmetic **nanodispersion**

AB . . . as fat-sol. vitamins, therapeutic oils, and sunscreen agents are solubilized for use in aq. cosmetic prepns. by formation of a **nanodispersion** with a combination of a polyoxyethylenesorbitan partial fatty acid ester, .gtoreq.1 phospholipid, EtOH, and H2O. The dispersion is only slightly turbid, has a **nanoparticle** size <60 nm, and is stable for several months during storage at room temp. Thus, a vitamin E **nanodispersion** was prepd. by dissolving 1.000 wt. part Lipoid S 100 in 0.650 part EtOH, adding 1.350 part Polysorbate 80 and. . . to 94.701 parts H2O contg. 0.272 parts NaH2PO4.2H2O, and stirring for 2-3 h at 200-300 rpm until the mixt. became **transparent** and slightly opalescent.

ST cosmetic **nanodispersion** Polysorbate phospholipid

IT Essential oils
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(bitter almond; cosmetic **nanodispersion**)

IT Cosmetics
(cosmetic **nanodispersion**)

IT Essential oils
Fat-soluble vitamins
Lysophosphatidylcholines
Lysophosphatidylinositols
Lysophospholipids
Phosphatidic acids
Phosphatidylcholines, biological studies
Phosphatidylglycerols
Phosphatidylinositols
Phospholipids, biological studies
Soya lecithins
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cosmetic **nanodispersion**)

IT Fats and Glyceridic oils, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(currant, Ribes nigrum seed; cosmetic **nanodispersion**)

IT Sunscreens
(lipid-sol.; cosmetic **nanodispersion**)

IT Lysophosphatides
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(lysophosphatidylglycerols; cosmetic **nanodispersion**)

IT Fats and Glyceridic oils, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(macadamia nut; cosmetic **nanodispersion**)

IT Disperse systems
(nano-; cosmetic **nanodispersion**)

IT Cosmetics
(sprays; cosmetic **nanodispersion**)

IT 58-95-7, .alpha.-Tocopherol acetate 64-17-5, Ethanol, biological studies
79-81-2, Vitamin A palmitate 81-13-0, D-Panthenol 5466-77-3, Parsol MCX 9005-63-4D, Polyoxyethylenesorbitan, fatty acid esters
9005-65-6, Polysorbate 80
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cosmetic **nanodispersion**)